PHYSIOLOGIC CONTROL OF ARTERIAL PRESSURE*

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MOST physicians are well aware of the different factors that enter into the control of arterial pressure, such as nervous factors, body fluids, and abnormalities of kidney function. However, understanding the manner in which all of these fit together for moment-by-moment, day-by-day, and month-by-month control of arterial pressure is generally hazy, not only in the minds of practicing physicians but also in the minds of research workers in this field. This presentation is an attempt to fit these factors together in an orderly manner, even though at the outset it must be clear that many of the problems of regulating arterial pressure are yet to be resolved.

The arterial pressure control system is multifaceted. Part of the system deals with acute control of arterial pressure from second to second, part of it controls pressure for intermediate periods of time such as minutes or hours, and still other parts have to do with setting the base level of arterial pressure day after day and month after month. In general, the nervous factors that affect arterial pressure operate over a period of seconds, minutes, and hours, while the renal and fluid and electrolyte factors play major roles in long-term regulation of arterial pressure over periods of days and months. Therefore we shall separate our discussion of arterial pressure control into 1) acute and semiacute control, and 2) long-term control.

Acute and Semiacute Control of Arterial Pressure

ACUTE CONTROL BY NERVOUS FACTORS

We need not spend much time in discussing the nervous factors that control arterial pressure because these are widely understood.

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Therefore let us simply list the different nervous mechanisms with some degree of annotation.

Baroreceptors. The baroreceptors, located in the carotid sinuses, in the arch of the aorta, and in a few other isolated areas of the large arteries of the upper thorax and neck, become excited when the arterial pressure rises. These then transmit signals to the vasomotor centers of the brain to cause reflex decrease in activity of the heart and reflex vasodilation throughout the body. Therefore, a rise in arterial pressure causes a secondary decrease in the pressure back toward normal. This is called a *negative feedback control system.*

Two aspects of baroreceptor control deserve special mention. First, the baroreceptors can moderate pressure changes by approximately 60 to 80%;[1] that is, some extraneous factor that tends to increase the arterial pressure above normal will increase it 60 to 80% less if the baroreceptors are functioning than when the baroreceptors are not functioning. Thus, instead of the pressure rising perhaps 100 mm. Hg after sudden infusion of fluid, it will rise instead only 20 to 40 mm. Hg.

Second, the baroreceptors adapt,[2] which means that if they continue to be stimulated over a long period of time by elevated pressure, their signal output gradually fades back to its normal level. This adaptation has a half-time of approximately one to two days, which means that at the end of only a few days the baroreceptors are not at all useful in signaling to the brain that an abnormal pressure is present. Because of this adaptation the baroreceptors are useful for control of arterial pressure only for minutes and hours but not for days.

Chemoreceptors. Located in association with the baroreceptors in the thorax and neck are small globular bodies supplied by minute arteries; these contain nerve receptors called chemoreceptors that are responsive to changes in oxygen and carbon-dioxide concentrations in the blood. When the arterial pressure falls below approximately 80 mm. Hg, the chemoreceptor cells become very active and transmit signals to the brain to cause reflex increase in activity of the heart and reflex vasoconstriction. Therefore in the lower pressure ranges, below approximately 80 mm. Hg, the chemoreceptors become a very important part of the nervous control system for arterial pressure. The degree of moderation of pressure changes is probably about the same as the degree of moderation caused by the baroreceptors, except that the baroreceptors operate in the pressure range between approximatly 80 mm. Hg

and 180 mm. Hg while the chemoreceptors operate in the pressure range between approximately 80 mm. Hg and 40 mm. Hg.

Ischemia of the central nervous system. Located in the vasomotor center of the medulla are nerve cells that are directly sensitive to ischemia. Therefore, when the arterial pressure is greatly reduced, which causes reduced flow of blood to the neuronal cells of the vasomotor center, these cells become excessively active and excite activity in the heart while also causing intense peripheral vasconstriction, thereby elevating the pressure.

The response of the central nervous system to ischemia has almost no degree of arterial pressure control activity until the arterial pressure falls below 50 to 60 mm. Hg; then it becomes intensely active as the pressure falls into the range of 20 to 30 mm. Hg.[3] Indeed, in this range it has the capability of moderating pressure changes more than 90%, which makes it a far more powerful pressure controller in the pressure range of 20 to 30 mm. Hg than are the baroreceptors in the normal pressure range of around 100 mm. Hg. Yet this pressure control mechanism can be called the "last ditch stand" because it is almost never active under normal pressure control situations—only when a person is nearly at the lethal level of arterial pressure and has only a short time to live unless treatment is instituted immediately. It is probable that this mechanism has saved the lives of many persons in imminent danger of death from hemorrhage.

Shifts in Capillary Fluid as a Means of Moderating Changes in Arterial Pressure

Every physician is familiar with the fact that severe hemorrhage is usually followed by absorption of fluid from the tissue spaces into the blood, which increases the blood volume back toward its normal level. Likewise, many experiments have demonstrated that overtransfusion is followed within minutes by loss of much of the excess fluid into the tissue spaces. Therefore movement of fluid outward or inward through the capillary membrane can help to moderate changes in pressure. For instance, if a factor has caused the arterial pressure to rise far above normal and the capillary pressure shares in this rise, fluid will begin to move outward through the capillary membrane immediately and will continue to be lost until the capillary pressure returns essentially

to normal. When this has occurred, the arterial pressure likewise will have returned at least part way toward normal if not all the way.

Stress Relaxation and Reverse Stress Relaxation of the Circulatory System

Another mechanism that helps to compensate for changes in blood volume, a mechanism almost completely unknown by practicing physicians, is circulatory stress relaxation and reverse stress relaxation.[4] If the circulatory system is filled with an excess of blood, the resultant excess pressures throughout the system cause a slow stretch of essentially all vessels of the body, but especially of the veins and the venous reservoirs such as the liver and the spleen. Therefore, in effect, the circulatory system simply enlarges enough to make up for the increased blood volume.

Conversely, when hemorrhage occurs, the diameters of the vessels gradually shrink, especially the venous reservoirs such as the liver and the spleen, and in a short time the size of the circulatory system again more nearly fits the volume of blood that is available to fill it.

The mechanism of stress relaxation and reverse stress relaxation begins to act within seconds, and it continues to act over a period of hours or even days, but most of the effect occurs within approximately the first 20 minutes. Therefore this mechanism also is primarily a semiacute controller of arterial pressure. Indeed, it is not a long-term regulator of pressure at all, because the blood volume eventually adjusts itself to fill the capacity of the system however large the system has become or however small it has become, as will be discussed in the following sections of this paper in relation to long-term regulation of arterial pressure.

Long-Term Regulation of Arterial Pressure: Preponderant Role of the Kidney

Probably none of the control systems already discussed plays any significant role in long-term regulation of arterial pressure. The reasons for this are 1) the baroreceptors, on the basis of all knowledge presently available, finally adapt completely and therefore cannot be the basis for a long-term regulatory system; 2) fluid volume shift through the capillary walls and the stress relaxation mechanism cannot be long-term regulators of pressure because the mechanisms that regulate blood volume finally adjust it to the capacity of the vascular sys-

tem, altogether independently of shifts in capillary fluid or stress relaxation, which means that these two mechanisms can play only transient roles; and 3) the chemoreceptors and the response of the central nervous system to ischemia, though perhaps capable of maintaining their degrees of activity at least partially for long periods of time, do not function significantly at normal levels of arterial pressure, but act only at reduced levels of arterial pressure when the person is in danger of dying anyway.

Therefore, the mechanisms for regulation of arterial pressure day in and day out and month in and month out seem to be mainly independent of the nervous system and mainly independent of mechanisms intrinsic in the vasculature. On the other hand there is abundant clinical experience and experimental evidence which demonstrate that long-term regulation of arterial pressure is probably vested almost entirely in the kidney.

Therefore, the question that we must resolve is: How does the kidney exercise this long-term control of arterial pressure? And there are two major theories widely extant for explaining the role of the kidney in the regulation of arterial pressure: the humoral theory and the fluid and electrolyte theory.

The Humoral Theory of Control of Arterial Pressure by the Kidneys

The humoral theory of control of arterial pressure by the kidneys is really a conglomerate of many different theories, none of which has received complete substantiation but several of which are strongly proclaimed by many investigators.[5] The two major theories are: 1) the vasoconstrictor or renin-angiotensin theory, and 2) the renin-angiotensin-aldosterone-fluid and electrolyte theory.

The vasconstrictor or renin-angiotensin theory. Most physicians are familiar with the renin-angiotensin-vasoconstrictor theory for regulation of arterial pressure, particularly as it relates to hypertension. This theory states simply that a decrease in arterial pressure causes the juxtaglomerular apparatus of the kidneys to secrete *renin.* The renin in turn causes one of the proteins of the plasma to be converted into angiotensin. Angiotensin then has a direct vasconstrictive effect on the arterioles, thereby raising the arterial pressure toward normal. One can readily see that this, like the baroreceptor mechanism discussed earlier, is

a negative feedback control system whereby a fall or a rise in arterial pressure sets off a sequence of events that returns the pressure toward its original level. Unfortunately, measurements of renin and angiotensin in the blood have failed to show even a fraction of the amounts of these two substances necessary for this constrictor mechanism to be significant as a normal regulator of arterial pressure. Perhaps the mechanism does function as the cause of some types of hypertension, but even this is in doubt.

The renin-angiotensin-aldosterone-fluid and electrolyte theory. According to this theory, which has gained wide credence in the last few years, low arterial pressure causes the kidneys to secrete renin in the same manner as that discussed above; the renin in turn causes formation of angiotensin. The angiotensin then stimulates the adrenal cortices to secrete aldosterone, which in turn causes the kidneys to retain electrolytes and water. Thus, the fluid volumes of the body increase, and especially the sodium content of these fluids increases. It is presumed that the increased fluid or sodium in some way causes increased pressure, either by altering the hemodynamics of the circulation in consequence of altered blood volume or by causing arteriolar vasoconstriction.

Data have been accumulating within the last year which at least partially, if not completely, refute the renin-angiotensin-aldosterone-fluid and electrolyte theory. For instance, Blair-West and his colleagues[6] in Australia have removed the adrenal glands and then constricted the renal arteries while the animals were receiving steroid supportive therapy. Under these conditions the angiotensin could not possibly have altered the rate of secretion of aldosterone by the adrenal glands, since the adrenal glands were absent. Nevertheless, elevated pressure developed in precisely the same manner as in nonadrenalectomized animals. This demonstrates the unimportance of the mechanism in raising arterial pressure when blood flow through the kidneys falls too low.

The Renal-Fluid Volume Concept of Pressure Control

Pressure Regulation

It is therefore evident that each of the humoral theories for regulation of arterial pressure has weaknesses; indeed, as we shall show later, there is much reason to believe that all theories that purport to

explain control of arterial pressure through alterations of total peripheral resistance encounter basic theoretical objections. Let us now discuss mechanisms by which changes in body fluids and electrolytes might play significant roles in the regulation of arterial pressure.

Sodium ion is the one electrolyte that almost all research workers consider in relation to arterial pressure regulation because many conditions that cause sodium retention are associated with elevated arterial pressure. Such conditions include primary aldosteronism, renal disease that causes sodium retention, and, in experimental animals, simple excess sodium feeding. Yet, despite this association of sodium with hypertension, it has been very difficult to specify a mechanism by which sodium could raise pressure. One suggestion that has gained wide favor is that excess sodium in the body might cause an increased concentration of sodium in the vascular wall, where it has a direct vasoconstrictor effect on the arterioles. However, experiments have shown that renal disease sometimes causes greater retention of water than salt so that the sodium concentration in the blood actually becomes subnormal rather than supernormal even in the presence of marked hypertension. It is difficult to see how an excess of sodium could accumulate in blood vessels under these conditions. Accordingly this theory also encounters objections.

Therefore the electrolyte constitution of the blood has not yet been proved to be a factor in the control of arterial pressure, despite a number of interesting suggestions that electrolytes might play roles.

The Renal Fluid Volume Concept of Pressure Control

In our discussion thus far we have had difficulty in pointing out any single mechanism that has been proved to play a role in the long-term regulation of arterial pressure. However, there is one basic mechanism for pressure control observed by the physician day in and day out that can hardly be doubted; this is fluid-volume control of arterial pressure. To give an example, when a person bleeds severely, the blood volume obviously decreases and the arterial pressure also falls very low. In consequence of the low pressure, the kidneys retain fluid; this increases the blood volume toward normal, thereby also raising arterial pressure toward its normal value. This mechanism is not doubted by anyone, and all aspects of fluid retention that follows hemorrhage have been substantiated by experiment. Yet, strangely enough, many

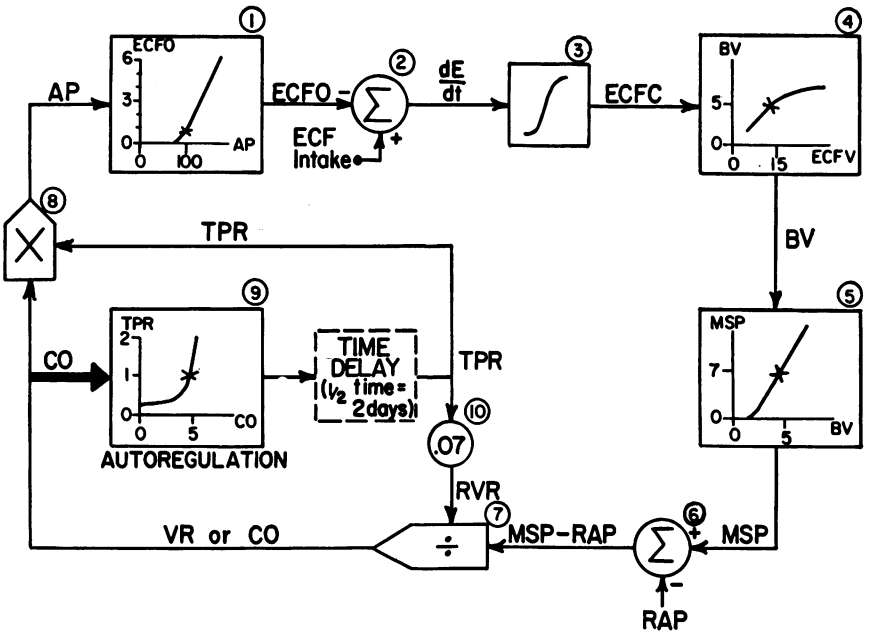

Fig. 1. A basic schema for regulation of arterial pressure by the renal-fluid volume mechanism. Symbols are as follows: *AP*, arterial pressure; *ECFO*, extracellular fluid output; *ECF*, extracellular fluid; dE/dt, rate of change of extracellular fluid volume; *ECFV*, extracellular fluid volume; *BV*, blood volume; *MSP*, mean systemic pressure; *RAP*, right atrial pressure; *VR*, venous return; *CO*, cardiac output; *TPR*, total peripheral resistance; *RVR*, resistance to venous return.

experimentalists in the field of arterial pressure regulation, and especially in the field of hypertension, relegate this basic renal-hemodynamic mechanism to a position of little importance in comparison with humoral factors of various kinds. However, we wish to indicate how important this basic renal fluid volume mechanism of arterial pressure regulation might be.

The basic renal fluid volume arterial pressure control circuit. Figure 1 is a systems diagram of the mechanism by which the kidney can regulate arterial pressure through the medium of fluid volumes.[7] Such a diagram is a modern way of expressing physiological mechanisms in definitive quantitative terms. Each part of this diagram has been substantiated by experiment; hence it deserves serious consideration. Let us explain it as follows:

Block 1 shows the effect of arterial pressure (AP) on renal output of extracellular fluid (EFCO), which means principally the effect of

arterial pressure on urinary output. Note that as the arterial pressure rises, the output of extracellular fluid increases sharply.

Block 2 shows subtraction of extracellular fluid output from extracellular fluid intake (ECF intake) consisting primarily of water and salt in the diet. The resultant effect is the rate of change of the extracellular fluid volume (dE/dt).

Block 3 shows the accumulation of extracellular fluid volume (ECFV); that is, integration of the rate of change of extracellular fluid gives the extracellular fluid volume at any given instant in time.

Block 4 illustrates the approximate relation between extracellular fluid volume and blood volume (BV) in the normal human and shows that an increase in extracellular fluid volume from the normal value of 15 l. up to approximately 22 l. is associated with an almost proportionate increase in blood volume. However, beyond 22 l. essentially all additional extracellular fluid accumulates in the tissues, and almost none remains in the blood.

Block 5 shows the relation between blood volume and the degree of filling of the circulatory system, expressed in terms of the so-called *mean systemic pressure* (MSP). This is the pressure in the circulation when all pumping of blood by the heart ceases and the pressures everywhere in the system have been brought to equilibrium.

Block 6 shows the subtraction of right atrial pressure (RAP) from mean systemic pressure to give mean systemic pressure minus right atrial pressure. Experiments have demonstrated that flow of blood from the peripheral circulatory system toward the heart is directly proportional to mean systemic pressure minus right atrial pressure.

Block 7 shows division of mean systemic pressure minus right atrial pressure by resistance to venous return (RVR), giving as its output venous return (VR), which is also equal to the cardiac output (CO). That is, resistance in the veins and other vessels of the peripheral circulation impedes return of blood toward the heart.

Block 8 shows multiplication of cardiac output by total peripheral resistance (TPR) to give arterial pressure.

Blocks 9 and 10 will be discussed later.

Note that the circuit in Figure 1 is also a negative feedback control system. If the arterial pressure rises too high, loss of extracellular fluid from the body eventually causes the arterial pressure to fall toward its normal level. Or if the arterial pressure falls too low, retention of fluid

causes the arterial pressure to rise toward normal. The different blocks in Figure 1 have been explained in detail in a previous publication,[7] and they have been substantiated by experimental data from our own and other laboratories.

Importance of autoregulation in the regulation of arterial pressure. One of the major problems in validating the mechanism of Figure 1 lies in Blocks 9 and 10. Without these two blocks the concept states that any factor that causes fluid retention in the body will increase the extracellular fluid volume, the blood volume, the mean systemic pressure, venous return, cardiac output and, finally, arterial pressure. However, in testing this mechanism experimentally one finds that persistent retention of fluid causes the arterial pressure to rise but may not increase the cardiac output. Therefore further exploration of the concept has indicated that an important part of it is the autoregulation mechanism.[7, 8]

The autoregulation phenomenon is well known to all physicians, but it is known by other names. It means simply that the local tissues automatically and intrinsically adjust their own blood flows in proportion to their needs. The mechanism can also be described in another way: When excess blood flows through a tissue area, the resistance of its vessels increases until the flow returns essentially to normal. Or if flow through the tissue falls too low, the resistance decreases until flow approaches normal. This effect is illustrated in Block 9 of Figure 1, which simply shows that a very slight increase in cardiac output above the normal value of 5 l. per minute causes marked increase in total peripheral resistance while a very slight fall in cardiac output causes marked fall in total peripheral resistance. If this mechanism is as important as some experiments indicate, an increase in cardiac output causes arterial pressure to rise for two reasons, first, because of the direct effect of increased cardiac output and, second, because of the indirect effect of increasing total peripheral resistance. When these two are multiplied together at Block 8 they give a disproportionate increase in arterial pressure over and above the increase in cardiac output. And the degree of this disproportion is directly proportional to the steepness of the curve in Block 9.

Two other features must be understood relative to the autoregulatory mechanism. First, only a small portion of the autoregulation occurs within the first few minutes, and the major share of it seems to

take place over a period of days or weeks. This long-term effect is what clinicians have frequently called vascularization or devascularization of a tissue in which the blood flow has been respectively too low or too high. Therefore the full effect shown in Block 9 does not take place within the first few hours but occurs gradually over a period of days and weeks. This should be remembered because experimental results to be discussed shortly seem to be explained by this mechanism only.

The second feature of the autoregulatory process is that an increase in total peripheral resistance not only increases arterial pressure but also increases the resistance to the return of blood from the systemic circulation to the right heart. Thus, Block 10 shows that an increase in total peripheral resistance increases the resistance to venous return; this in turn reduces venous return and cardiac output toward normal. Therefore, it would be expected that an increase in fluid volumes would initially increase the cardiac output and this would increase the arterial pressure. Then as the process of autoregulation takes place the arterial pressure would remain elevated or even rise still more because of progressive increase in total peripheral resistance while at the same time the cardiac output returns toward normal because of an increase in resistance to venous return.

Experimental tests of the renal fluid volume mechanism for pressure control. In recent experiments we have caused animals to retain large amounts of water and salt and thereby increase their fluid volumes.[9-11] This has been achieved by first removing 70% of the renal mass (one whole kidney and the two poles of the second kidney) and then feeding these animals normal saline in place of their usual drinking water. The results of these experiments have corresponded in almost minute detail with the basic mechanisms shown in Figure 1. They have occurred in two distinct phases as follows:

First phase, which develops over a period of two to three days:

1) Twenty per cent increase in blood volume, 30% increase in extracellular fluid volume, and 4 mm. Hg increase in interstitial fluid pressure.

2) Three mm. Hg increase in right arterial pressure.

3) Thirty per cent increase in venous return and cardiac output.

4) Twenty-five mm. Hg increase in arterial pressure by the second to third day.

Second phase, which occurs during next 10 to 20 days:

1) Progressive increases in total peripheral resistance to about 50% above normal.

2) Twenty-five mm. Hg further increase in arterial pressure, reaching a sustained plateau 50 mm. Hg above control in about 10 days.

3) Progressive decrease in cardiac output back to within a few per cent of normal by the end of 10 days.

4) Decrease in extracellular fluid volume and interstitial fluid pressure toward normal from approximately the fifth day to the 14th day.

5) Decrease in blood volume from a high of about 20% above normal at seven days to a sustained level of about 6% above normal at the end of three weeks.

Thus the results of these experiments have demonstrated transient overshoots in fluid volumes and cardiac output; these effects begin before the total peripheral resistance begins to rise. Then as total peripheral resistance increases, presumably as a result of autoregulation, cardiac output and fluid volumes return toward normal, while the arterial pressure rises still higher. The final result is elevated arterial pressure and elevated total peripheral resistance; other parameters of circulatory function measure within the normal ranges. Yet study of the transients at the onset of the change in arterial pressure demonstrates very forcefully that the initiating event of the pressure change was an increase in volume followed by an increase in cardiac output.

A simplified description of the renal fluid volume mechanism for pressure control. Though it has been important to present each of the steps in Figure 1 to portray the basic physiology involved, one can understand the concept of renal-fluid volume control of arterial pressure very readily by referring to Figure 2. This illustrates two curves drawn on the same graph. The solid curve shows the approximate effect of arterial pressure on output of extracellular fluid through the kidneys; this includes output of both water and salt. It illustrates that relatively slight increases in arterial pressure cause very marked changes in fluid output.

The second curve of Figure 2, the horizontal dashed curve, simply expresses the normal intake of extracellular fluid, including both water and salt. It is axiomatic that there is only one point on this graph at which these two curves can operate together, and that is where the two curves cross, called the "equilibrium point" in the figure. This

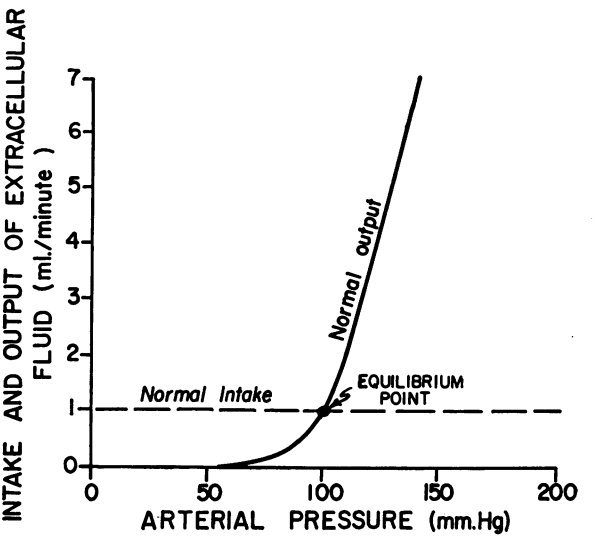

Fig. 2. Equilibration of the normal renal function curve for output of extracellular fluid with the normal curve for intake of extracellular fluid.

graph merely restates the well understood fact that fluid output must eventually come to equilibrium with fluid intake. Any time the arterial pressure falls so low that the intake of fluid is greater than output, arterial pressure will rise until the kidneys increase their output to equal intake. Conversely, if the arterial pressure becomes too high, output becomes greater than intake, and renal loss of fluid volume eventually allows the arterial pressure to fall back to that level which will barely give an output equal to intake. Thus the arterial pressure is adjusted automatically to the point at which the two curves in Figure 2 cross: that is, the equilibrium point.

Figure 3 shows how these concepts apply to several abnormal conditions of renal function. Note that the normal renal function curve and the normal intake curve cross each other at equilibrium point A. Now let us see how abnormal conditions affect the equilibrium.

1) *Excess intake of water and salt in a normal person.* The upper horizontal dashed curve of Figure 3 represents a two and one-half times increase in extracellular fluid intake, which corresponds to eating about 15 gm. of salt per day and drinking an equivalent amount of water. Note that the new equilibrium point becomes point B, which predicts an arterial pressure rise of about 10 mm. Hg, an amount that is hardly

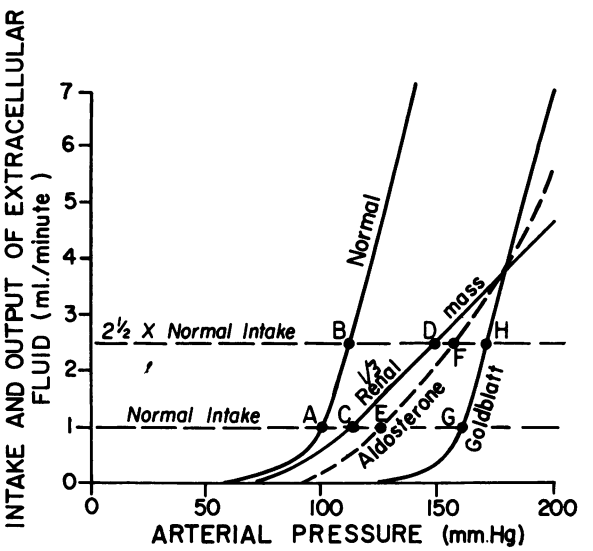

Fig. 3. Equilibration of output and intake of extracellular fluid in a human being with various renal abnormalities.

detectable by usual clinical methods. This, indeed, is the usual experience.

2) *Decreased renal mass.* The seond renal function curve of Figure 3 is for a person whose renal mass has been decreased to one-third normal. This equilibrates at point C with the normal intake curve, which indicates that a person with approximately one-third normal functioning renal mass should have an arterial pressure increase of about 10 mm. Hg above normal. In a series of dogs in which this set of conditions was created, we measured an actual increase in pressure of 7 mm. Hg. When extracellular intake is increased to two and one half times normal, the renal function curve equilibrates with the intake curve at point D, which indicates that the arterial pressure should rise to a mean value of approximately 148 mm. Hg. In a series of dogs in which these conditions were created, the arterial pressure increased to an average value of 145 mm. Hg.

3) *Excessive aldosterone effect on the kidneys.* The third curve of Figure 3 illustrates the renal function curve after injection of a large dose of aldosterone (as extrapolated to the human being from data obtained in dogs). One can see that it takes greatly increased pressure to

cause the kidney to excrete water and salts under these conditions. The renal function curve equilibrates with the normal intake curve at point E, which indicates that prolonged infusion of aldosterone, such as occurs in primary aldosteronism, might increase the arterial pressure by about 25 mm. Hg which, indeed, is very commonly the case. Point F shows equilibration of the aldosterone curve with an elevated water and salt intake curve; this indicates that a combination of aldosteronism with intake of excess water and salt might give excessive elevation of mean arterial pressure to above 150 mm. Hg.

4) *Goldblatt kidneys.* Figure 3 illustrates the calculated renal function curve for Goldblatt kidneys in the human being: severe constriction of both renal arteries. This curve shows the kidneys to be as functional as ever except that it takes an arterial pressure increased by 60 mm. Hg to cause the same output from the Goldblatt kidneys as from the normal kidneys. Or to state this another way, there is a 60 mm. Hg pressure drop through the constricted arteries. The Goldblatt renal function curve equilibrates with the normal intake curve at point G, which gives an arterial pressure of 160 mm. Hg. Intake of excessive amounts of water and salt increases the pressure (point H) only another 10 mm. Hg. This is precisely the result that has been achieved by many different research workers in relation to salt loading of Goldblatt animals, namely, a change in salt intake makes little difference in the level of pressure.

Thus it is evident that almost all aspects of pressure regulation by the renal fluid volume pressure control mechanism can be predicted from the simplified diagrams of Figures 2 and 3, in which renal function curves for output of extracellular fluids at different arterial pressures are equated against intake of extracellular fluid. However, it must be recognized that these states of equilibrium do not come about rapidly. Indeed, when the function curve of the kidney is suddenly changed, as by the application of Goldblatt clamps, the full state of equilibrium usually is not achieved for several weeks because of the necessity for fluid and salt to be retained, for hemodynamic adjustments to occur in the circulatory system, and for the phenomenon of autoregulation to become fully developed. Therefore the renal fluid volume control mechanism is very slow to act, even though at least some evidence indicates that it is very powerful once it does act. Its slowness probably accounts for the fact that it is not a widely acclaimed mechanism among physi-

ologists who work in the field of blood-pressure regulation or in the field of hypertensive studies.

Computer Studies that Indicate the Unimportance of Total Peripheral Resistance in Control of Arterial Pressure or in the Genesis of Hypertension:

Two basic facts of clinical medicine long ago indicated that changes in total peripheral resistance ordinarily do not alter the long-term regulated level of arterial pressure. These are:

1) A chronic arteriovenous fistula, which often causes the total peripheral resistance to fall as low as one-half normal, does not cause the arterial pressure to fall even perceptibly, except acutely. Indeed, when such a fistula is created, the pressure falls only a few mm. Hg but returns to its original level within a few days. Therefore it is evident that this large change in total peripheral resistance does not alter the long-term controlled level of arterial pressure.

2) A person with all four limbs amputated often has a total peripheral resistance 50% above normal. Yet here again the arterial pressure is absolutely normal.

These two facts are so well documented that it is difficult to understand how the concept has permeated medicine that arterial pressure is controlled primarily by changes in total peripheral resistance. However, the reason for this is that *acute* changes in total peripheral resistance do indeed cause such changes in arterial pressure. If the basic mechanism shown in Figure 1 is reexamined, it becomes clear that acute experiments cannot be extrapolated to the long-term state.

In previous computer studies we have analyzed the effects of many different stresses on the circulatory system, utilizing a basic circuit design similar to that in Figure 1 but with other aspects of circulatory function also built in[7-12] – such aspects as: 1) the baroreceptor feedback control system, 2) the chemoreceptor feedback control system, 3) dynamics of the heart under both normal conditions and conditions of failure, 4) the renin-angiotensin system for control of blood pressure through both the mechanism of vasoconstriction and the mechanism of fluid electrolyte retention, and 5) other factors, e.g., interstitial fluid dynamics. These computer analyses were discussed previously and are much too complex to present here, but we present one example of the results. Figure 4 shows the computed effects on arterial pressure, blood

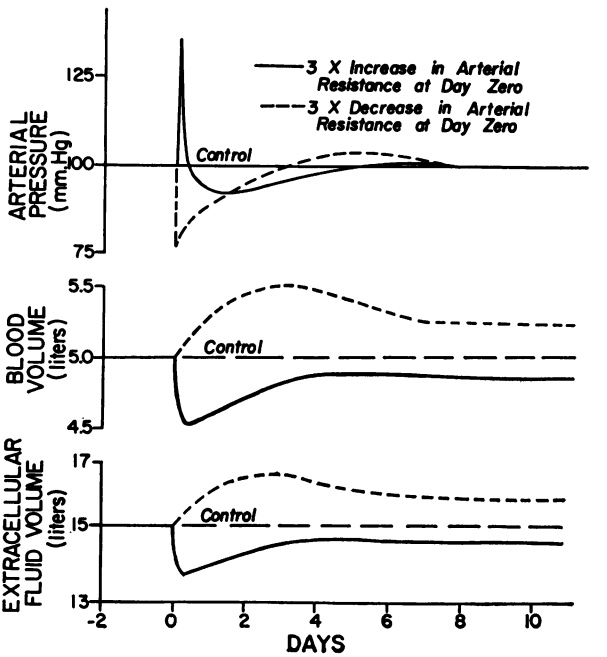

Fig. 4. Computer predictions of changes in circulatory function when total peripheral resistance is suddenly increased threefold or decreased threefold but without altering renal resistances. Reprinted by permission of the American Heart Association, Inc., from: Guyton, A. C. and Coleman, T. G. A quantitative analysis of the pathophysiology of hypertension. *Proc. Amer. Heart Ass. Council for High Blood Pressure Research,* Cleveland, 1968. In press.

volume, and extracellular fluid volume caused by either 1) a threefold increase in total peripheral resistance at day zero but with the resistances in the kidneys remaining unchanged, or 2) a threefold decrease in total peripheral resistance at day zero but with the resistances in the kidneys remaining unchanged. Note that from the solid curves, representing the threefold increase in resistance, it is predicted that this will cause an instantaneous and very significant increase in arterial pressure. However, the extracellular fluid volume and blood volume immediately begin to decline because of marked loss of fluid through the kidneys. Therefore it is predicted that within approximately 10 to 12 hours the arterial pressure will have fallen back to normal, and that within 6 to 8 days the pressure will have become equilibrated precisely at the normal value. Exactly opposite results occur when resistance is decreased. In support of these predictions are numerous studies on

arteriovenous fistulas. Opening an arteriovenous fistula can decrease the total peripheral resistance exactly as simulated in Figure 4. Further, the results—increased fluid volumes and return of arterial pressure to normal within a few days—are precisely those predicted by the computer. When the fistula is closed, the resistance increases and reverse events ensue, as predicted.

Therefore evidence at present indicates that changes in total peripheral resistance, when they do not affect resistance to blood flow through the kidneys, have no long-term effect on the regulation of arterial pressure.

Importance of renal resistance to the regulation of arterial pressure, in contrast to total peripheral resistance. If the renal resistance is increased, particularly afferent arteriolar and arterial resistance, the renal function curve will be shifted far to the right in the manner shown in Figure 3 for the Goldblatt kidney. Therefore changes in renal resistance exert the most profound possible effects on long-term regulation of arterial pressure. This is in contradistinction to the effects of resistance changes elsewhere in the body. Therefore, both on theoretical grounds and on experimental observations—especially with A-V fistulas —one can state with reasonable certainty that we should not be concerned with total peripheral resistance per se as one of the factors important in the control of arterial pressure; instead we should be concerned with changes in renal resistance.

There are many other possible factors in the circulatory system that might affect renal resistance: for instance, angiotensin formed in one kidney could easily cause increased renal resistance in the opposite kidney, which means that a damaged kidney on one side of the body could cause retention of water and salt by the opposite kidney.

Another method by which renal resistance can be altered is through the nervous system, either as a result of direct sympathetic impulses to the kidney or through neurohumoral mechanisms. Further, neurohumoral mechanisms, such as the ADH mechanism or the aldosterone mechanism, can alter the renal function curve without changing renal resistance but by changing reabsorption of water and salts by the renal tubules.

Thus there are many different ways in which the renal-fluid volume mechanism for arterial pressure control can be affected secondarily by: 1) the nervous system, 2) the endocrine system, and 3) other con-

ditions in the body. But nevertheless, most data at present point to the kidney as the most important final arbiter in determining the long-term basal level of arterial pressure.

Summary

In this discussion of the physiologic regulation of arterial pressure it has been pointed out that acute regulation is vested primarily in: 1) the nervous system, 2) the shift of fluid between interstitial spaces and blood, and 3) the stress-relaxation mechanism of the vascular system. However, these factors, even including the nervous system, seem to be unimportant for long-term regulation of arterial pressure. Almost all evidence at present indicates that regulation to be vested almost entirely in the kidneys.

Perhaps the most prevalent theory for pressure control by the kidneys is the renin-angiotensin theory, which holds that low pressure causes production of angiotensin, which then elevates arterial pressure toward normal either as a result of vasoconstriction throughout the body or by promoting the secretion of aldosterone, which in turn causes fluid retention. However, several facts cannot be explained by this mechanism, including the fact that changes in total peripheral resistance, such as those that result from arteriovenous fistulas, do not cause changes in arterial pressure. Also, arterial pressure can be regulated normally even when the adrenal cortices are prevented from changing their rate of aldosterone secretion.

The renal fluid volume concept of arterial pressure regulation has been discussed in detail in this paper. It is pointed out that retention of water and electrolytes by the kidneys causes a slow increase in arterial pressure, and that this increase results initially from an increase in cardiac output. However, the phenomenon of autoregulation then secondarily increases the total peripheral resistance while returning cardiac output to its original mean level. This theory of regulating arterial pressure is receiving more and more experimental support.

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